Long Term Sequela of Pediatric Bladder Reconstruction

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Abstract
Children with refractory neurogenic bladder (NGB) who have failed maximal medical management are presented with options for bladder reconstruction. It is critical to understand the long-term sequela of bladder augmentation and bladder neck reconstruction to properly counsel families regarding these procedures. Benefits may include preservation of renal function, continence, reduced risk of renal-related mortality and potential improvements in quality of life (QOL). However, these advantages must be balanced with the risks of bladder calculi, perforation, need for additional surgery, acid/base disturbances, vitamin B12 deficiency and malignancy. Therefore, careful patient selection and preoperative counseling are paramount for those undergoing bladder reconstruction which includes intestinal bladder augmentation, as these patients require lifelong vigilant follow-up.

Introduction
Children with neurogenic bladders (NGB) are initially managed with clean intermittent catheterization (CIC) and anticholinergic medications in order to maintain a sizable, continent, and compliant urinary reservoir. Despite early and aggressive intervention, some patients undergo lower urinary tract reconstruction (bladder augmentation, catheterizable channel and/or bladder neck reconstruction) to protect their upper tracts and achieve continence. In a few select patients with favorable urodynamics (UDS) and low outlet resistance, a bladder neck procedure (BNP) can be performed without bladder augmentation to achieve continence. Myelodysplasia, specifically spina bifida (SB), remains the most common etiology of NGB in the pediatric population. Due to medical advances, particularly in the realm of Urology, more SB patients with bladder reconstruction are surviving into adulthood. We review current literature regarding long-term sequela of bladder reconstruction in pediatric patients with neurogenic bladder, with a primary focus on bladder augmentations for refractory NGB secondary to SB.

Bladder augmentation, the interposition of a piece of compliant tissue such as small bowel, large bowel, stomach, or ureter onto the native bladder, improves compliance by increasing bladder capacity and decreasing storage pressures. Despite bladder augmentation serving as the gold standard for refractory NGB, most research has focused on its complications rather than its benefits. Improvement in continence, bladder capacity and upper tract preservation has been documented, however, scare published data exists regarding impact on QOL or overall renal function following bladder augmentation.

Benefits
The primary aim of bladder reconstruction is to improve both capacity and compliance. Poor bladder compliance leads to increased hydrostatic pressure during storage of urine which over time may lead to renal damage and renal failure, particularly with storage pressures > 40 mmH2O (1). In addition, bladder augmentation, by reducing storage pressure, has been shown to improve urinary continence, decrease hydronephrosis and resolve low grade vesicoureteral reflux (VUR).

Reduction in the Incidence of Renal Failure
Following introduction of the ventricoperitoneal shunt (VPS), renal failure became the leading cause of mortality in the SB population, responsible for 25-30% of deaths beyond infancy (2). Renal function is typically normal at birth and deteriorates secondary to the abnormal physiology of NGB, however recent studies suggest that this deterioration is preventable. Szymanski et al. found renal failure as the cause of post-augmentation mortality in only 0.5% of SB patients who underwent bladder augmentation at 10 years (3). Compared to previously published rates, this data demonstrated a significant reduction in mortality due to renal failure in a cohort at high risk for developing renal failure. The authors' conclusions are supported by a separate, modern era,

cohort of 120 SB patients, where no deaths were due to renal failure by age 20 (4). Furthermore, for patients managed with gastrocystoplasty due to poor renal function at the time of augmentation, most showed preserved or improved renal function (5). While studies appear to demonstrate that renal failure mortality is reduced in SB patients who have undergone bladder augmentation, there is no case-control data available revealing a renal failure mortality benefit of bladder augmentation.

Continence/Bladder Capacity/Upper Tract Preservation
Bladder augmentation improves urinary continence, bladder capacity, and preserves the upper tracts by reducing vesicoureteral reflux and hydroureteronephrosis secondary to poor compliance. (6-10). Krishna et al. found no evidence of progressive renal scarring or upper tract deterioration following bladder augmentation (10). Bladder augmentation with a concomitant bladder neck procedure results in a urinary continence rate ranging from 67-94% depending on the type of bladder neck reconstruction and length of follow-up (11-14).

Urinary Tract Infections
Diagnosing clinically significant urinary tract infections (UTIs) following bladder augmentation is often exceptionally difficult. Nearly all patients with augmented bladders must catheterize to empty, which results in bacterial colonization and asymptomatic bacteriuria. In addition, bacterial colonization of the augmented bowel segment is essentially universal and chronic. Thus, the diagnosis of UTI must incorporate a high index of clinical suspicion (fevers, new or worsening incontinence, foul odor, hematuria) in conjunction with a positive urine culture. In spite of this diagnostic dilemma, Krishna et al., have shown a reduction in the incidence and severity of UTIs following bladder augmentation (10).

Quality of Life
Bladder reconstruction has demonstrated positive effects on QOL including improved self-image and self-esteem (15). This impact has been questioned recently when MacNeily et al. failed to show any improvement in overall QOL following bladder augmentation in SB patients (16, 17). Importantly, the QOL instrument used by MacNeily et al. does not specifically ascertain the impact of fecal or urinary continence. These studies emphasize the need for utilization of specific, validated QOL instruments to accurately assess bowel and bladder function in this patient population.

One such potential health-related QOL instrument has recently been developed and validated. QUAlity of Life Assessment in Spina Bifida in Adults (QUALAS-A) was created with participation of individuals with SB, their families and experts in SB care and has demonstrated excellent reliability and validity (18), Pediatric and teenage age-specific versions of QUALAS are undergoing validation at this time. As a SB-specific instrument, QUALAS may prove decidedly useful in clinical and research settings.

Risks
Although bladder reconstruction imparts multiple benefits, these are weighed against significant long-term risks, including calculi, acid/base disturbances due to absorption of urine by bowel, bladder perforation, B12 deficiency, and increased risk of malignancy. Despite advances in tissue engineering, variations in bowel substrates used to augment the bladder, and improvements in surgical techniques, the ideal tissue and technique for bladder reconstruction remain elusive (5, 19, 20). Furthermore, the ideal age to undertake bladder reconstruction also remains unclear, as patients 3-5 years old showed similar complications and reoperative risk compared to older patients (21).

Bladder reconstruction should be considered a permanent alteration to the lower urinary tract requiring close and lifelong observation. In the largest published series, complications were observed in 169 of 500 bladder augmentations (34%) resulting in an additional 254 surgeries, for a cumulative risk of further bladder-level surgery of 0.04 operations per patient per year following bladder reconstruction (22). However, two-thirds of patients with bladder augmentations did not require additional procedures during the time frame of the study.

Bladder Calculi

Bladder calculi often require operative intervention and are diagnosed in 11 – 52% of patients after bladder augmentation (22-26). Calculi typically form in bladders augmented with ileum and/or colon, when absorbable staples are used, in the setting of incomplete bladder emptying, and in patients with a metabolic predisposition for stone formation (hypocitraturia). Bladder calculi are rare in gastric augments (5, 27-29). Other factors shown to increase risk of bladder calculi include: recurrent urinary tract infections, non-compliance with catheterizations or irrigations, and poor adherence to follow-up (30, 31). It is a common belief that bladder calculi share an infectious etiology; however, 30% have been found to be non-infectious (32). Several factors may contribute to stone formation, including chronic metabolic acidosis, resultant chronic kidney disease, and hypercalciuria related to wheel-chair dependence related osteodystrophy. Recent evidence by Kisku, et al. revealed exstrophy/epispadias and recurrent UTIs as independent risk factors for developing bladder calculi in patients with bladder augmentations (33).

Studies revealed a median time to stone formation of 37.5 months (range 11-120 months) (33) and a high recurrence rate after treatment. Indeed, between 15-29% of bladder calculi recur in less than 2 years (24). Depending on stone size and burden, multiple treatment modalities exist, ranging from endoscopic management to open cystolithotomy. Endoscopy for appropriately sized stones has demonstrated high rates of stone clearance with a low rate of complications (33) while preventing morbidity of entering the abdominal cavity. However, endoscopy via channel or urethra may result in injury to the channel or to a reconstructed bladder neck. It has been reported that surgical technique did not affect rate of bladder calculi recurrence (27, 28). This was recently confirmed by Szymanski, et al., who found that bladder stones recurred in almost half of patients within nine years following initial stone surgery independent of treatment modality or patient characteristics (36).

The authors remove the majority of bladder stones through endoscopic, percutaneous or laparoscopic access, although approach is dependent on stone size, number, history of bladder neck procedure and presence of a catheterizable channel. After stone removal, patients undergo a 24 urine collection and analysis, and evaluation in a multidisciplinary stone clinic to facilitate coordinated management with Urology and Nephrology (36).

Metabolic Derangements

Bowel segments continue their absorptive capacity despite being incorporated into the urinary tract, which may lead to metabolic derangements. Metabolic acidosis is relatively rare in patients with normal renal function who have undergone a bladder augmentation associated with use of a small bowel segment (37, 38). Hyperchloremic metabolic acidosis occurs with ileal and/or colonic segments secondary to the loss of bicarbonate and potassium. This process results from the reabsorption of ionized ammonium and chloride; ammonium is exchanged for a hydrogen proton, bicarbonate is exchanged for a chloride ion. Ionized ammonium can then be absorbed into the blood through potassium channels (39). Hypochloremic hypokalemic metabolic alkalosis can occur with the use of gastric segments (5) and hyponatremic hypochloremic hyperkalemic metabolic acidosis develops with the use of jejunum (40).

Chronic metabolic acidosis can lead to decreased bone mineral density and has raised concern for impaired linear growth following bladder augmentation in children; however, no studies have validated this theoretical complication (41). It remains feasible that prolonged acidosis may lead to osteomalacia or osteoporosis in adulthood (42). Metabolic acidosis should be corrected when diagnosed and patients provided calcium and vitamin D supplements. In some cases, bisphosphonates may become necessary to prevent loss of bone mass (41, 43-45).

Perforation

The utmost morbid and catastrophic complication following bladder augmentation is perforation, which may culminate in peritonitis, sepsis and even death. Reported rates of bladder perforation following augmentation range between 6-13% (9, 22, 46-49). Perforation occurs due to increased intravesical pressure, which may result from chronic bladder over-distention, chronic infection, traumatic catheterization, and ischemic necrosis of the intestinal segment used for the augmentation (50-56). Bladder perforation usually demands exploratory laparotomy with externalization of VPS (if present), to reduce the risk of CNS infections. In select patients without VPS, conservative management with catheter drainage, percutaneous drains, and close monitoring can be successful (57).

In the largest published series, 43 out of the 500 patients (8.6%) who underwent bladder augmentation suffered a perforation. Increased risk of perforation was associated with the use of non-detubularized sigmoid colon, presence of a bladder neck procedure, and history of prior bladder perforation, while presence of a continent catheterizable channel was protective for perforation. Bladder perforation remains a lifelong risk following bladder augmentation, with one third occurring within 2 years, another third between 2 and 6 years, and the final third occurring after 6 years following initial surgery (22).

Physicians must possess a high clinical suspicion for a perforated bladder augmentation due to impaired sensation in spina bifida patients. A detailed history, physical examination to assess for peritonitis, and laboratory analysis including white blood count and serum creatinine are useful when diagnosing bladder perforation. Patients with history of bladder augmentation who present with acute abdominal pain, poor urine output, elevated serum creatinine, and elevated white blood count should be urgently evaluated for possible bladder perforation. A low-pressure CT cystogram, including post-drainage film, remains the gold standard for diagnosing bladder perforation by evaluating for contrast extravasation into the peritoneal space (22, 55).

Vitamin B12 Deficiency

Hypocobalaminemia, or vitamin B12 deficiency, defined as a serum B12 concentration less than 200 pg/mL, can occur after bladder augmentation with symptoms ranging from occult to dramatic. Patients with hypocobalaminemia may present with pernicious anemia, characterized by megaloblastic anemia, gastrointestinal symptoms, and potentially irreversible neurological symptoms including peripheral neuropathy, loss of positional and vibrational sense, ataxia, seizures, and dementia (58, 59). The risk of hypocobalaminemia is thought to increase approximately 5 years after augmentation and continues to escalate over time (60, 61).

Vitamin B12 can be replaced parenterally or orally. Oral replacement is generally well-tolerated and effective in increasing serum B12 levels for the short term, however, long-term oral replacement success is poor, possibly due to reduced patient compliance (62, 63). Fortunately, hypocobalaminemia is often asymptomatic but the potentially devastating, irreversible neurologic complications make its diagnosis and treatment essential. A review of 23 patients

with augmented bladders with serum B12 levels <300 pg/mL revealed no evidence of pernicious anemia at a mean of 49 months following initial abnormal B12 level (63).

Our practice advocates checking serum B12 annually in patients starting 5 years after bladder augmentation. Patients with serum B12 levels <100 pg/mL are initiated on parenteral replacement therapy and referred to neurology. Patients with serum B12 levels <300 pg/mL are started on oral replacement therapy with a daily multivitamin containing 250 mcg B12. Serum B12 levels are then reassessed every 3 months. If hypocobalaminemia persists, the patient is converted to parenteral therapy. Patients who respond well to oral replacement are monitored annually and converted to a parenteral replacement if hypocobalaminemia recurs.

Malignancy

Cancer in augmented bladders is an ever-present concern (64-72), confirmed by several large series reporting an incidence ranging from 1.1-4.5%. Soergel et al. reported urothelial carcinoma in 3/260 patients who underwent bladder augmentation for neurogenic bladder with at least 10 years follow up (69). Husmann and Rathbun found a 4.5% incidence of bladder cancer in 153 bladder augment patients with a minimum of 10-year follow-up. Higher rates of bladder cancer were associated with well-known carcinogenic stimuli, e.g., prolonged tobacco exposure, chronic immunosuppression, and bladder exstrophy (73). Patients with gastric augmentation appear to develop tumors more frequently and earlier after surgery compared to patients with ileal augmentation. If this association is due to the interposition of a gastric segment, or because gastrocystoplasty was preferred in a high risk population, i.e., patients with renal failure and/or renal transplant, remains unclear (70, 72).

Interestingly, patients with neurogenic bladder managed solely with clean intermittent catheterization have also demonstrated an increased risk of bladder cancer, and this risk may be increased following bladder augmentation (74).

Some physicians recommend yearly endoscopy for potential early detection of malignant bladder tumors in the augment population (13, 75-77). However, others argue that yearly endoscopy is not cost effective and the potential morbidity makes it an ineffective screening procedure (78, 79). A decision analysis performed by Kokorowski et al. determined that annual screening cystoscopy and cytology were not cost-effective (80). Higuchi et al. have recommended cystoscopy in patients with four or more symptomatic UTIs per year, gross hematuria, microscopic hematuria with 50 or more RBC/hpf, abnormal radiographic screening studies, chronic perineal, pelvic or bladder pain, and for patients with colonic augments age 50 or older (consistent with colonoscopy recommendations) (79, 81). Any significant change in a patient's baseline function may merit investigation with anatomic or functional studies for this vulnerable population at the clinical discretion of the Urologist.

Catheterizable Channels

Catheterizable channels are often created concomitantly to bladder augmentation procedures to facilitate ease of intermittent catheterization for patients with limited mobility and dexterity. Channels may be created from appendix (appendicovesicostomy, APV) or a segment of tubularized ileum (Monti ileovesicostomy), both of which have a low rate of stomal stenosis at <10%, and a high rate of continence at > 95%. While stomal stenosis, stomal revision procedures and channel continence were similar between APV and Monti channels, patients who underwent Monti catheterizable channels were twice as likely to require subfascial revision at 10 years follow-up. The longer spiral Mmonti channels to the umbilicus carried the greatest requirement for subfascial revision (82, 83). Complications continued to arise over the lifetime of the channel. Channel creation can increase a patient's ability to discretely and independently

empty their bladder, however, just as with any bladder reconstruction, patients and families must be appropriately counseled of the long-term risks and benefits of this procedure.

Bladder Neck Procedures

Bladder neck reconstruction is often used to manage urinary incontinence; however, multiple types of bladder neck repairs have been utilized with variable success rates. Szymanski, et al. reported that the Kropp (n=38) and Salle (n=12) urethral lengthening procedures both displayed durable long-term outcomes with follow up of 6.9 and 10.3 years respectively. Kropp and Salle procedures attain 75-78% continence at greater than 4 hour intervals and 88-94% at greater than 3 hour intervals. The majority of patients with these types of bladder neck reconstructions did not require any additional procedures for continence (84).

Although primarily used in the exstrophy-epispadias population, the Young-Dees-Leadbetter (YDL) repair also has reported adequate long-term continence rates. In a cohort of 38 patients, Donnahoo, et al. found that 30 patients were continent and 7 patients were partially continent. In this cohort, 26 patients required only one procedure, while 8 required 2 procedures and 3 required more than 2 procedures to achieve continence (85). More recently, it has been shown that quality of life in female patients who have undergone a YDL repair is similar to a normal population (86).

Bladder neck slings (BNS) and artificial urinary sphincters (AUS) are also feasible options for treatment of sphincteric dysfunction. After an average of 4.2 years, 51 of 58 patients had achieved continence after a rectus fascia BNS (87). Small intestinal submucosal bladder neck slings achieve satisfactory rates of continence (>75%) at a mean of 15 months follow up in 14/18 females and 75% of non-ambulatory males who underwent concomitant bladder augmentation and catheterizable channel. Ambulatory males achieved a lower rate of continence (2/5, 40%) with bladder neck slings (88). Artificial urinary sphincters, unlike other bladder neck procedures, may still allow for spontaneous voiding in the neurogenic bladder population. In 134 patients with AUS, continence was achieved in 86% and continence improved in an additional 4%. Approximately 25% of this population spontaneously voided, while the remainder required clean intermittent catheterization to fully empty their bladder (89).

Isolated Bladder Neck Procedures

Due to the long-term sequela of bladder augmentation, some urologists perform isolated bladder neck procedures in appropriately selected patients with low bladder outlet resistance. Studies have suggested that isolated bladder neck procedures without augmentation are safe in carefully selected patients.

Snodgrass et al. initially reported a series of 75 BNPs without augmentation and 4 years of follow up in which 23% of patients developed hydronephrosis and 25% developed vesicoureteral reflux. The authors reported all cases of hydronephrosis resolved with medical management, while persistent reflux was managed with ureteral injection or re-implantation (90). However, an update of this cohort reveals 54% required additional continence procedures with 18% requiring augmentation cystoplasty, 46% developing vesicoureteral reflux/hydronephrosis and 21% developing newly diagnosed or worsening renal scarring. Upper tract changes, incontinence and elevated bladder pressures improved in all patients following augmentation cystoplasty (91).

In contradistinction, a series of 15 consecutive patients who underwent isolated bladder neck repair all eventually underwent salvage bladder augment (92). Finally in another series of 29 patients with a mean follow-up of 8 years who underwent isolated BNP, Whittam et al. reported

delayed augment in 45% of patients at an average of 34.4 months (3-117 months) (93). Clearly, these studies demonstrate the need for close, life-long follow-up if isolated bladder neck procedures are performed. In select instances, such approaches appear to be safe and effective while avoiding the morbidity associated with a bladder augmentation in nearly half of patients.

Current Long Term Management Strategy

At our institution, all pediatric SB patients with bladder reconstruction are followed in our multidisciplinary SB clinic, with adult patients evaluated in the transitional urology clinic. Annual renal bladder ultrasound is used to monitor upper tracts, with urodynamics reserved for patients who develop hydronephrosis (new or worse) or new incontinence to ensure adequate capacity of the augmented bladder. Annual laboratory studies include a complete blood count and basic metabolic panel, with the addition of serum B12 measures beginning five years post-operatively. We encourage patients to perform daily bladder irrigations with normal saline to help prevent formation of bladder calculi. Lastly, we review the patient's catheterization schedule to identify and address any new or evolving difficulties.

Conclusion

Bladder reconstruction, including bladder augmentation, for refractory neurogenic bladder remains a mainstay of therapy for patients failing conservative management. Bladder reconstruction improves continence and protects upper tracts from deterioration due to a high-pressure bladder, which can reduce renal failure and mortality. Such reconstructions can additionally may improve a patient's quality of life.

However, bladder reconstruction carries considerable lifelong risks. Thus, it should only be pursued in appropriately selected patients after considerable counseling. Risks of bladder calculi, metabolic derangements, perforation, hypocobalaminemia, and malignancy must be explained in detail to the patient and their family. While there are significant benefits to performing bladder reconstruction, the long-term sequela of the surgery mandate a lifelong commitment from the patient, family, and their urologist.

Compliance with Ethics Guidelines

Conflict of Interest

Joshua Roth, Alison Keenan, Mark Cain and Benjamin Whittam declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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